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Recent Progress in Histamine H_3 Receptor Chemistry

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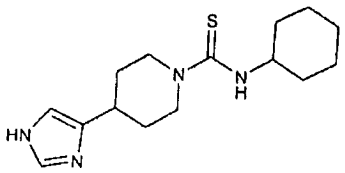
1. INTRODUCTION

It has been over twenty years since the pioneering work of Arrang and co-workers demonstrated that histamine inhibited its own release from rat brain cortical slices via a novel receptor that is pharmacologically distinct from both the H_1 and H_2 receptors [1]. It is now well recognized that this third histamine receptor, the H_3 receptor, is a G-protein coupled receptor that functions both as an autoreceptor, controlling the release of histamine from histaminergic neurons, as well as a heteroreceptor, controlling the release of other neurotransmitters such as serotonin and noradrenalin. In the intervening years since the discovery of the H_3 receptor, considerable effort has gone into preparing novel H_3 receptor ligands and the field has evolved from one dominated by imidazole-derived analogs, with their attendant pharmacokinetic and toxicological issues, to one in which there are now several classes of non-imidazole compounds. Additionally, the potential therapeutic utility of these molecules in the treatment of disease, particularly CNS related disorders, is now starting to be tested in human clinical trials. The goal of this report is to update the current state of the field of H_3 receptor medicinal chemistry.

2. NON-IMIDAZOLE H_3 RECEPTOR ANTAGONISTS

The imidazole analog thioperamide, 1, was the first selective H_3 antagonist identified [2], and most of the early literature in the field described compounds that were

candidates for a number of reasons. For example, the imidazole moiety is an excellent ligand for the iron present in the heme group of the cytochrome P450 isozymes. Consequently, many 4-substituted imidazole analogs are potent inhibitors of these critical metabolic enzymes [3]. Additionally, the H_3 receptor is located primarily in the CNS and most of the proposed therapeutic applications for agonists and antagonists are in the treatment of CNS-related diseases. Therefore, good brain penetration is imperative for activity. However, many imidazole containing analogs do not display high brain levels due to the hydrogen bond donor and acceptor properties of the imidazole ring [4].



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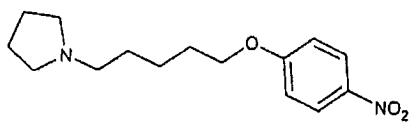
As a result of these issues, a significant amount of effort has been expended by a number of research groups in academia and industry on identifying ligands for the H_3 receptor that do not incorporate a 4-substituted imidazole ring. This work eventually led to the identification of the phenolic ether class of H_3 receptor antagonists, exemplified by **2**, as the first potent, non-imidazole H_3 receptor antagonist [4]. The general structure given by **2**, a tertiary amine, preferably cyclic, tethered to a phenolic ether via a hydrophobic chain is a common pharmacophore for the H_3 receptor, and this motif is repeated in a number of different series of compounds from several labs.



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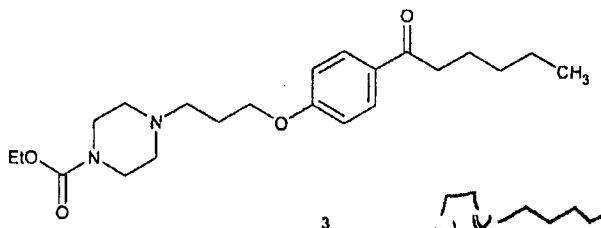
For example, high throughput screening of the Abbott compound collection led to the identification of the piperazine amide A-923 (**3**) as a high affinity ligand ($K_i = 2$ nM) for the rat H_3 receptor although it displayed poor oral bioavailability and selectivity [5].



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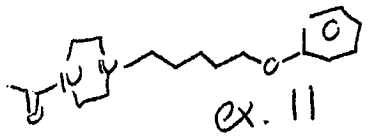
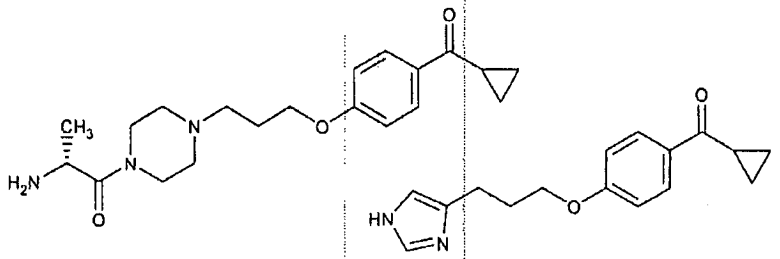


ex. 11

Systematic optimization of this lead led to the identification of a cyclopropyl ketone series exemplified by **4** [6]. Interestingly, this series of analogs incorporates the same tail group as ciproxifan (**5**) so it appears that the piperazine amide may be acting as a surrogate for the imidazole ring. Like ciproxifan, compound **4** was a more potent ligand for the rat full-length receptor than for the human full-length receptor and acts as an inverse agonist [7]. Compound **4** was also active in a variety of *in vivo* CNS models [8]. For example, rat pups treated with **4** (10 mg/kg, s.c.) showed improved cognitive performance in an avoidance test while social memory was improved in adult rats treated with 3 and 10 mg/kg, i.p. [8].



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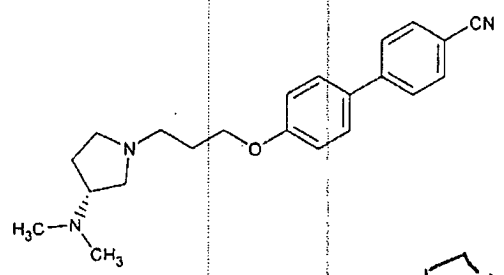
Further work in this series identified the biphenyl nitrile **6** [9]. Unlike the piperazine amide **4**, this compound is a potent ligand for both the rat and human H_3 receptor ($pK_{i\ rat} = 7.87$, $pK_{i\ human} = 8.56$) and is selective for the H_3 receptor over the H_1 and H_2 receptors. Furthermore, **6** was the first non-imidazole H_3 antagonist to show weight loss in a diet-induced obesity model [10]. In a 28-day study in mice fed a high fat diet, **6** (15 mg/kg) reduced weight to a level comparable to mice fed a low fat diet. Total body fat as measured in the fat pads was reduced and the animals displayed normal insulin tolerance. Consistent with a central mode of action, **6** attains extremely high concentrations in the brain (brain/plasma = 160 at 1 h following 5 mg/kg i.v. administration).



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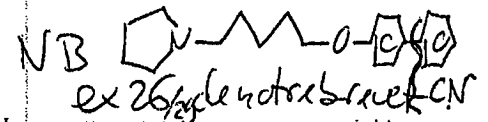
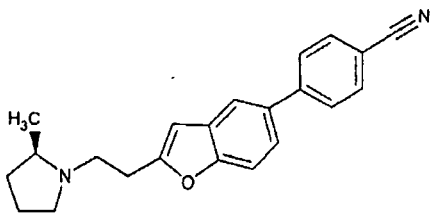


This lead structure was further optimized. In an attempt to prepare more rigid analogs and thus potentially improve the pharmacokinetic and selectivity profiles of the series, benzofuran analog **7** was obtained by cyclization of the alkyl ether chain back onto the central phenyl ring [11]. Compound **7** is a potent ligand for the human and rat H_3 receptors ($K_i = 0.45$ and 3.22 nM, respectively) and displays excellent brain concentrations after i.v. dosing (brain/plasma > 30). This compound is reported to be in Phase I clinical trials for the treatment of cognition related disorders.



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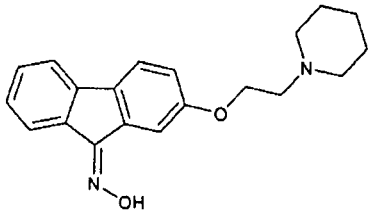
This privileged H_3 pharmacophore has appeared in several other series of H_3 receptor ligands. Oxime **8** is structurally related to **6** in that the biphenyl moiety of **6** is now linked via a five-membered ring. In this case, the *Z*-oxime is essential for good H_3 activity ($K_i = 65$ nM). The *E*-oxime is approximately tenfold less active [12]. Imidazopyridine **9**, which was also derived from a lead identified via high throughput screening, is a potent ligand for the human H_3 receptor ($K_i = 2$ nM) with good selectivity over the H_1, H_2, and H_4 receptors as well as more than 50 other biogenic amine and neuropeptide receptors. Compound **9** also displayed good oral pharmacokinetics after dosing in the rat [13]. Sequential removal of each of the nitrogen atoms of **9** gives either an indolizine or indole analog, respectively [14]. The indolizine analogs were more potent than the corresponding indoles with the 3-methyl analog **10** being equipotent to **9** ($K_i = 2$ nM).



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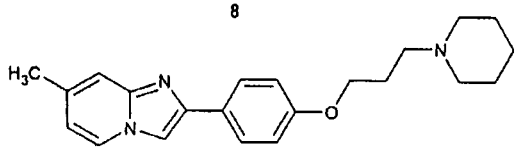

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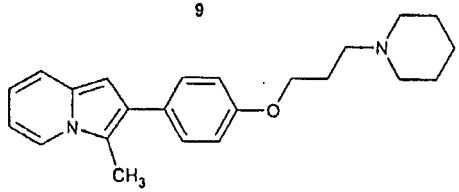

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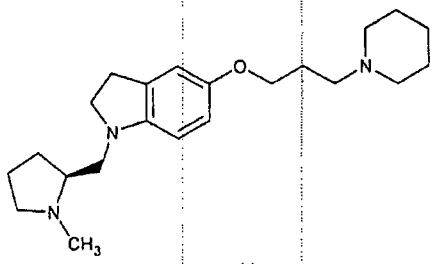
A number of other groups have also reported variations on this theme. For example,



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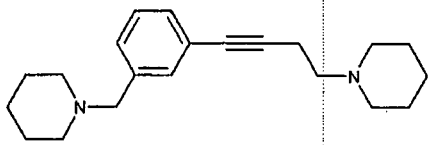
Not all non-imidazole H_3 antagonists fit this pharmacophore. A structurally related but novel series of piperidine alkynes exemplified by structure **12** has been prepared [16]. In this case an alkyne moiety has replaced the ether linker. Optimum binding activity seems to reside in those analogs with a basic tertiary amine on the 4-position of the butynyl chain. For example, compound **12** ($pK_a \approx 10.1$) binds to the H_3 receptor with subnanomolar affinity ($K_i = 0.8$ nM). The corresponding morpholine analog **13** ($pK_a \approx 7.4$) is a significantly weaker ligand ($K_i = 15$ nM). While the 4-position of the butynyl group seems to be sensitive to substitution, the 3-position of the central phenyl ring is more tolerant. For example, the left-hand piperidine of **12** can be replaced with the much bulkier indanyl amine as in **14** and still retain good binding affinity ($K_i = 1.3$ nM).



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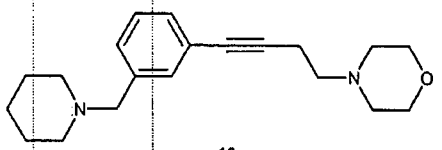

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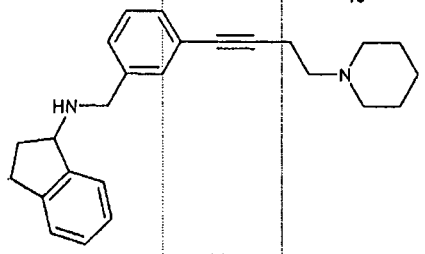

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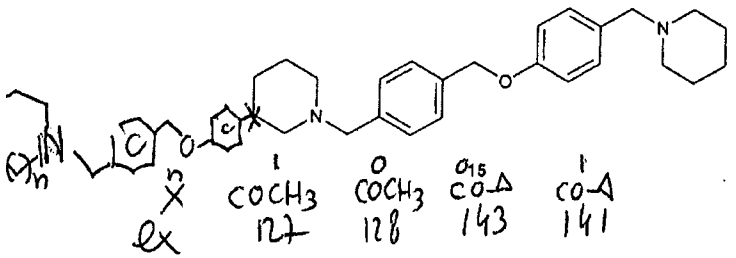
Pseudo-symmetric analog **15** represents another series of unique non-imidazole

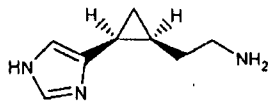
(K_i = 2.8 nM) although it was relatively weak *in vivo* in the mouse when dosed orally (ED_{50} = 9.6 mg/kg).

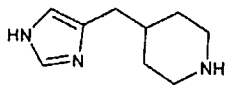


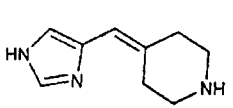
3. IMIDAZOLE DERIVED H_3 RECEPTOR AGONISTS AND ANTAGONISTS

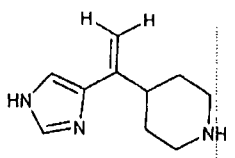
3.1. Selective H_3 receptor agonists

Although there has been noteworthy progress in the discovery of non-imidazole H_3 receptor antagonists, significant interest still exists in imidazole based analogs as well. The discovery of the histamine H_4 receptor which shares an overall 43% identity homology to the histamine H_3 receptor has rekindled interest in discovery of highly selective H_3 receptor ligands [18]. Recently, a cyclopropane-based conformationally restricted analog of histamine, **16**, was found to be a potent H_3 receptor agonist which exhibits very good binding affinity (K_i = 1.3 nM) and functional activity (EC_{50} = 10 nM) but has virtually no effect on the H_4 receptor [19]. SAR investigations on immepip **17** (pK_i = 9.32; pEC_{50} = 9.88), a potent H_3 receptor agonist of moderate selectivity (46 fold favoring the H_3 receptor), resulted in the identification of olefin analogs **18** and **19** which exhibit decreased affinity and functional activity at the H_3 receptor (pK_i = 8.23 and 8.40; pEC_{50} = 8.50 and 8.63, respectively) but increased selectivity for the H_3 receptor over the H_4 receptor (300 and 700 fold, respectively) [20]. Alternatively, replacement of the piperidine ring of **17** with a 4-pyridine resulted in the discovery of a potent and highly selective H_3 receptor agonist, immethridine **20** (pK_i = 9.07, pEC_{50} = 9.74), which exhibits 300-fold H_3 receptor selectivity over the H_4 receptor [21]. In the search for novel H_3 receptor agonists, which lack a basic moiety in the side chain of the molecule in order to improve pharmacokinetic properties, a novel chiral carbamate **21** was prepared. Compared to BP294, a prodrug of (*R*)-α-methylhistamine, compound **21** was significantly more efficacious in all tissues investigated in the capsaicin-induced plasma extravasation models in rats (ED_{50} = 0.07–0.1 mg/kg p.o.) [21,22].









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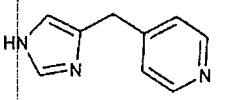

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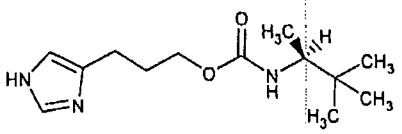

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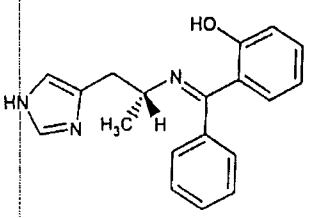
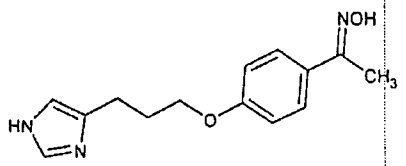


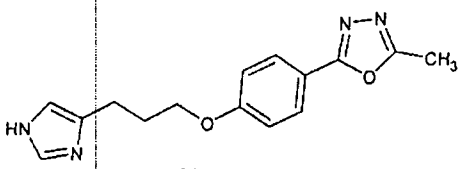
22 (BP 2-94) (R-)

3.2. Imidazole H_3 receptor antagonists

The proxifan class, compounds containing an imidazole heterocycle connected by a three-carbon alkyl chain to a *para*-substituted phenyl ether moiety, was previously reported to contain numerous potent and orally active H_3 antagonists, e.g., ciproxifan [5] (K_i = 0.49 nM; ED_{50} = 0.14 mg/kg p.o.) and imoproxifan (**23**) (K_i = 0.26 nM; ED_{50} = 0.034 mg/kg p.o. in mice) [23,24]. Recent work on the design of novel heterocyclic proxifan analogs has led to the identification of oxadiazole derivatives which displayed reduced potencies compared to those of ciproxifan and imoproxifan, but retain high *in vivo* efficacies, e.g., compound **24** (K_i = 13 nM; ED_{50} = 0.57 mg/kg p.o.) [25]. In an effort to discover a novel and selective H_3 antagonist that can be used in combination with an H_1 antihistamine for the treatment of nasal congestion, a novel series of H_3 receptor antagonists was prepared by incorporating urea and carbamate linkers to the 4-benzyl-(1*H*-imidazole-4-yl) template. The urea **25** is a potent H_3 antagonist (K_i = 4 nM) and it demonstrated excellent oral plasma levels in the rat (AUC = 18.1 μg h/ml at 10 mg/kg p.o.) and monkey (AUC = 12.6 μg h/ml at 3 mg/kg p.o.) [26].



23 (Imoproxifan)



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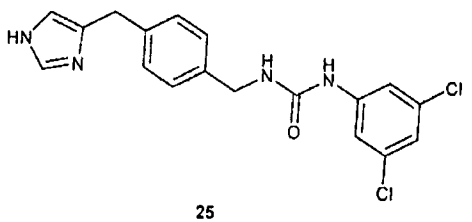

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4. HISTAMINE H_3 ANTAGONISTS WITH A DUAL MODE OF ACTION

Three series of compounds which combine H_3 antagonism and another pharmacological profile in one molecule were recently reported. In contrast to the combined application of two molecules, these hybrid molecules have the advantage of a single pharmacokinetic and toxicological profile. In search of novel ways to enhance histaminergic neurotransmission in the central nervous system, a novel class of aminoquinoline histamine H_3 receptor ligands was developed that simultaneously possessed strong inhibitory activity on the main histamine metabolizing enzyme, histamine *N*-methyltransferase (HMT) as well as H_3 antagonist activity. Non-imidazole **26** (K_i (H_3) = 0.09 nM; IC_{50} (HMT) = 51 nM) and imidazole **27** (K_i (H_3) = 4.1 μM; IC_{50} (HMT) = 24 nM) exhibit dual H_3 antagonistic and HMT inhibitory activity [27,28]. Combining the first generation H_1 antihistamine chlorpheniramine with H_3 ligands of the alkylamine type has led to the discovery of dual ligands of the H_1 and H_3 receptors, e.g., **28** (K_i (H_1) = 7 nM; K_i (H_3) = 15 nM). Compounds such as **28** may be useful for the treatment of allergies and nasal congestion [29]. Nitric oxide (NO) is a recently discovered endogenous messenger. There is strong evidence that furoxan system (1,2,5-oxadiazole, 2-oxide) is able to release NO under the action of thiol cofactors [30]. Consequently, a series of H_3 antagonists endowed with NO-donor properties were designed by coupling the H_3 antagonist SKF91486 with the NO-donor furoxan moieties. Although behaving only as a weak partial H_2 agonist, compound **29** ($pA_2(H_3)$ = 7.02; pD_2 = 5.28) was able to trigger a dual NO-dependent muscle relaxation and H_3-antagonistic effect on guinea-pig ileum [31].

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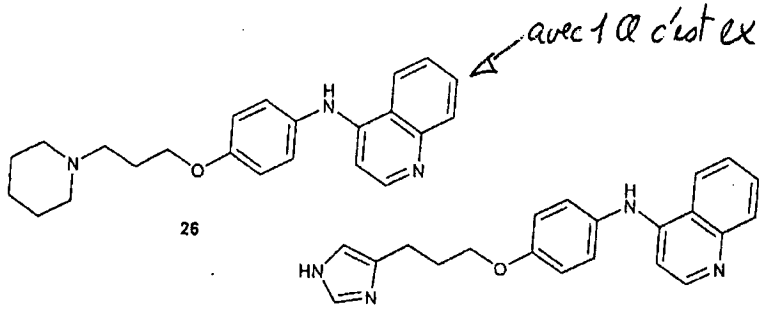

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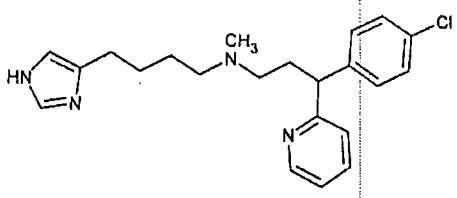

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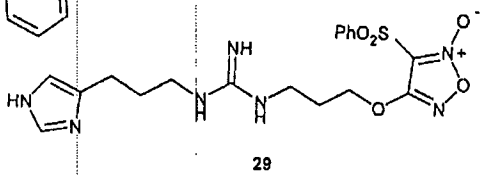

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Anti-Resorptive and Anabolic Bone Agents

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Contents

1. INTRODUCTION

Osteoporosis is a disease characterized by an increased risk of bone fractures that res
from reduced bone mass and bone strength [1–3]. In humans, bone mass is maintai
or increased through the balancing actions of continuous bone resorption and depositi
In healthy individuals, bone mass reaches a peak during early adulthood, and then beg
to slowly decline with advancing age. Women, who generally have lower peak b
mass than men, experience a more rapid loss of bone following menopause. T
accelerated loss of bone material is associated with an increasing risk of fracture o
time. In the United States, 10 million persons are estimated to have osteoporosis, an
total of 34 million have low bone mass, indicating increased risk of disease. T
estimated national direct expenditure for osteoporosis and associated fractures in 20
was 17 billion USD.

Osteoporosis therapy seeks to maintain or increase bone mass and strength so t
fracture risk is reduced. This can be done by decreasing the rate of bone resorpti
increasing the rate of bone deposition, or by a combination of both actions. Several no